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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,160	01/15/2007	Eric W. Brunskill	CHM-017	5911

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EXAMINER	
MONTANARI, DAVID A	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,160	BRUNSKILL ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-6 and 10-17 are examined in the instant application.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 6-8 that are cancelled have been renumbered as claims 7-9, though still cancelled.

Claim Rejections - 35 USC § 101/112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Definitions:
[from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf]

"Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a *specific* or *substantial* utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. 101. This analysis should, of course, be tempered by consideration of the context and nature of the invention. For example, if a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial *asserted* utility would be considered to be met.

See also the MPEP § 2107 - 2107.02.

Claims 1-6 and 10-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The instant specification discloses transgenic mice which have a disruption in an endogenous Npas3 gene (pg. 4 parag. 0012). The specification further teaches that the transgenic mice claimed exhibit a variety of behavioral phenotypes (pgs. 13-22). The specification further discloses that the claimed transgenic mouse will be useful for determining the effectiveness of a biologically active agent (pg. 4 parag. 0013). However, none of these asserted utilities of the claimed transgenic mouse, methods of use and isolated cell from said mouse demonstrates a substantial or specific utility.

At the time of filing, the skilled artisan would not have found such utilities evident because the specification only teaches general utilities that could apply to any knockout mouse. None of the utilities asserted in the instant specification are drawn to the disrupted Npas3 gene. The specification discloses no known function of the Npas3 gene. That a gene may be important in any biological function indicates no known function of said gene at the time of filing. Further, neither the specification nor the art at the time of filing taught a relationship between any behavioral phenotype and a deficiency in the Npas3 gene. Given the fact that the function of the Npas3 gene is unknown there can be no definitive correlation that the phenotypes recited in the claims are linked to the function of the Npas3 gene.

As set forth in the utility guidelines summarized above, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a

disclosure of what condition can be diagnosed. Similarly, a statement of therapeutic utility for an unspecified disease is non-specific rendering the purported utility for the claimed mouse to be non-specific. The usefulness of the mutant mice as models is not clear without assessing that they specifically reflect a disease state, leaving the skilled artisan to speculate the uses of the transgenic mouse, methods of use and cells of the claims. A search of the recent art provides no known function of the Npas3 gene and the specification further provides no known function for Npas3 (Brunskill et al. 1999, Mechanisms of Development, Vol. 88, pgs. 237-241). Brunskill only teaches that the Npas3 gene may be involved in neurogenesis (pg. 237 col. 2 parag. 1 last sentence). Additionally, the use of the claimed mice to determine a function for the disrupted gene Npas3 lacks a specific or substantial utility as further research on the mouse is required to determine if the changes in behavioral phenotypes observed are associated with the loss of the specific gene product or due to the methodology used in making the mice. Under the utility guidelines set forth above, requirement for further research or experimentation renders the claimed invention as lacking a specific or substantial utility. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. The evidence of record has not provided any other utilities for the transgenic mouse encompassed by the claims that are specific and substantial.

Since the mouse Npas3 gene and its relation to any disease or condition is unknown, and the increased insulin levels in mice comprising a disrupted Npas3 gene are not specific to any one disease or condition, the artisan at the time of filing would not know how to use the mice or any data resulting from using the mice to determine function for the mouse Npas3 gene product. To make such a determination, the skilled artisan would need to further research the mice to

determine the gene function of Npas3. Since the mice and the methods of using the mice lack a specific or substantial utility the cells claimed also have not utility. The utility of each of these is disclosed in the specification to be based on utility of the mice.

In light of the above, the skilled artisan would not find the asserted utility of the transgenic mouse, methods of using said mouse and isolated cells from said mouse to be specific and substantial.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 10-17 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence

of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompasses a transgenic knockout mouse which models schizophrenia

The claimed transgenic mouse, isolated cells and methods of using said cells and mouse all encompass and are drawn from the fact that the claimed transgenic mouse would be considered a model of schizophrenia based upon the disclosure in the specification. However, as the art below teaches, the successful modeling of schizophrenia is unpredictable and is compounded by the fact that significant variability exists in the phenotypes assayed in the claimed transgenic mouse and how they (the phenotypes) and the results reported would not be considered predictable measures that would indicate that a mouse is schizophrenic.

Unpredictability of Schizophrenia Animal Models:

With respect to mouse models of human neurological and psychiatric disease the art teaches that such models are unpredictable (1998, Picciotto et al., Physiological Rev., Vol. 78, pgs. 1131-1163). Picciotto teaches that "For many psychiatric diseases, which may have several causes, it is not possible to have one model that mimics all the aspects of the human disease. Accordingly, it may not be possible to know whether one has a schizophrenic mouse. Instead, it

might be possible to break down the human disease into cognitive and attentional deficits, negative symptoms, and psychosis, and perhaps individual mouse mutants can be developed that model particular subsets of symptoms of the disease" (pg. 1152, col. 2 parag. 2, lines 13-21). The knockout mouse in the claimed method is an asserted model of schizophrenia based upon the linkage of the Npas3 gene in diagnosed individuals that suffer from schizophrenia (pg. 4 parag. 0011). The question of Npas3's role in schizophrenia is not an issue of enablement, but rather the phenotypes recited in the claims and whether the phenotypes observed in the claimed transgenic mouse are related to a disruption in Npas3 or other factors such as background strain. The knockout mouse in the claimed method is said to exhibit many different phenotypes including parkinsonian gait of stride length and footprint pattern and dyskinesia of hindlimb and foot clasping posture. Psychosis is an attributable phenotype of schizophrenics, however the skilled artisan is lead to question whether the phenotypes embraced by the claimed method are 1) related to schizophrenic behavior, 2) associated with psychosis and 3) are the result of a disruption in the Npas3 gene.

Unpredictability of Background Strain:

The state of the art involving the creation of knockout mice teaches that genetic variables of the background strain of knockout mice significantly impacts resulting phenotype(s) (Linder C., 2006, ILAR Journal, Vol. 47, pgs. 132-140, see Abstract). Linder continues to teach that although some phenotypes due to specific mutation are found in all genetic backgrounds, phenotypic variability often becomes apparent only when a mutation is studied on numerous genetic backgrounds (pg. 136, col. 1 parag. 1 lines 3-6). Linder continues to teach that this type of modulation in a mutant phenotype is typically referred to as a genetic background effect, and

that another factor that contributes to variable and/or unexpected phenotypes observed in mutant mice is the inadvertent introduction of a hypomorphic, rather than a null, mutation. Linder details that a hypomorphic mutant gene displays a partial, rather than complete, reduction in the activity it influences and that alternately, there may be compensatory pathways in the mouse that are upregulated in the absence of a normally expressed gene (pg. 136 col. 1 parag. 1 lines 6-15). Linder continues to teach that an observed phenotype may be due to genes completely independent of the modified gene or transgene. Further, Linder continues that during congenic strain development, a gene linked to a modified gene may be carried over during backcrossing and contribute to the phenotype of the mouse (pg. 137, col. 1 last parag.). Linder summarizes that by observing a single phenotype in a knockout mouse considerable work still exists to be performed on the knockout mouse:

"Thus, to return to Dr. Musmusculus' euphoria upon discovering that one of his knockout mice has a phenotype, we recall that he immediately recognizes the necessity of answering "difficult questions." Despite a significant investment of time and skill (2 yr in gene targeting and chimeric mouse generation, and then another year to expand and age the knockout colony), he knows that still more work lies ahead before the genetic factors that influence his knockout mouse can be identified accurately. Only once that identification is complete will it be time to consider publishing the findings." (pg. 139 col. 1, parag. 4).

Thus while significant data and publications exist to the skilled artisan with regard to the creation of knockout mice, this work cannot be considered routine in view of the lack of teaching in the instant specification regarding the creation of the claimed knockout mice as detailed

further below. However, the art continues to teach a comprehensive analysis of how the genetic background of a mouse used in knockout studies significantly impacts the observed phenotype.

Variability of phenotype in knockout mice of different strains:

The art teaches that genetic background has a significant influence on hypertension and renal failure in COX-2 knockout mice (Yang T., 2004, Am J Physiol Renal Physiol, Vol. 288, pgs. F1125-F1132, see Abstract). Yang teaches that COX-2 was knocked out in three congenic strains of mice: 129, C57 and BALB (pg. F1126 col. 1 parag. 1). Yang continues that blood pressure was significantly increased in 129 compared to C57 and BALB (Fig. 1), urinary excretion of albumin was significantly increased in 129, somewhat in C57 and unchanged in BALB (Fig. 2), and abundant protein casts, dilated tubules and infiltration of inflammatory cells in the kidneys of 129 mice but not C57 or BALB strains (Figs. 3-5). Yang concludes that "the severity of the phenotype is significantly influenced by genetic background and gender" (pg. F1131 col. 1 parag. 2 lines 6-8).

The art continues to teach that the genetic background determines the extent of atherosclerosis in Apo-E knockout mice (Dansky HM, 1999, Arterioscler Thromb Vasc Biol, Vol. 19, pgs. 1960-1968, see Abstract). Dansky contrasts two strains of Apo-E knockout mice: C57 and FVB/NJ (pg. 1961, col. 1 parag. 2). Dansky continues to teach that "genetic background has a major effect on atherosclerosis susceptibility in two strains of ApoE-deficient mice. C57Bl/6J Apo-E deficient mice were much more susceptible to atherosclerosis than FVB/NJ Apo-E deficient mice" (pg. 1961 col. 1 parag. 2 lines 1-5). Dansky continues that FVB Apo-E deficient mice had higher total cholesterol, HDL cholesterol, ApoA1 and ApoA2 levels compared to C57 Apo-E deficient mice (pg. 1962, Table 1) and that mean aortic root

atherosclerotic lesion was 7- to 9-fold higher in C57 Apo-E mice compared to FVB Apo-E mice (pg. 1964, Fig. 2). Dansky concludes that the strain difference in the rate of atherosclerotic lesion development (which is a widely used assay in murine models of atherosclerosis, pg. 1965, col. 1 parag. 1 lines 12-15) is clearly genetic due to differences in genetic background (pg. 1966 col. 1 parag. 2).

Thus while Applicant has taught that transgenic knockout mice comprising a disrupted Npas3 gene exhibit a variety of phenotypes, the state of the art above would teach the skilled artisan that any phenotype observed in the claimed mice would be unpredictable and further provides significant doubt that the phenotype observed in the claimed mouse is actually resulting from the disruption in the Npas3 gene.

Variability of behavior phenotypes in mice of different strains:

The art continues to teach a concise review of the significant variability among mouse strains as well as the environment that they are tested in (1999, Crabbe et al., Science, Vol. 284, pgs. 1670-1672). Crabbe teaches that among eight strains of mice, A/J, C57BL/6J, BALB/cByJ, DBA/2J, 129/SvEvTac, 129/Sv-ter, 5HT1B -/-, and B6D2F2 a significant variation exists among said strains when evaluated in the open field test (Fig. 1), elevated plus maze (Fig. 2) and ethanol consumed (Fig. 3). Further three separate test sites (Portland, Edmonton, and Albany) were used to demonstrate that different test environments affect the behaviors observed. Crabbe concludes that "for behaviors with smaller genetic effects (such as those likely to characterize most effects of a gene knockout), there can be important influences of environmental conditions specific to individual laboratories, and specific behavioral effects should not be uncritically attributed to genetic manipulations such as targeted gene deletions" (pg. 1672, Col. 1 parag. 3, lines 10-18).

The art further illustrates the point of how different mouse strains affect anxiety-related behavior, locomotion and nociception (2004, Zimmer et al., Psychopharmacology, Vol. 176, pgs. 343-352). Zimmer teaches an in-depth comparison over a variety of common laboratory tests of two different strains of mice, C57BL/6J and DBA/2J which are homozygous knockouts for the Penk1 gene (Abstract, pg. 343). Zimmer continues that horizontal locomotor activity in an open field test was significantly different between C57BL/6J and DBA/2J knockout mice (pg. 345, Fig. 1). Zimmer continues that with regard to nociception the tail-flick latencies, hot-plate first sign of discomfort, hot-plate jump response and acetic acid-induced writhing were each different between C57BL/6J and DBA/2J knockout mice (pg. 346, Fig. 2 a-d). With regard to anxiety and social interaction Zimmer teaches that significant differences occurred between each knockout strain in the social interaction test (pg. 348, Fig. 5 a), startle response test (pg. 348, Fig. a-b), and acetic acid induced stress test (pg. 348, Fig. 7). Zimmer concludes in the discussion that genetic background revealed a profound influence on the Penk1 -/- phenotype (pg. 349, col. 2 parag. 2), and that in anxiety tests C57BL/6J and DBA/2J knockout mice differed for no apparent reasons other than they were from different strains (pg. 350, col. 2 parag. 2). Collectively Zimmer teaches that the strain of mouse used in a behavioral study has a material impact on the subsequent results.

The state of the art summarized above underscores the significant variability in phenotypes that exist among many of the strains of mice used in knockout studies. In mice without any genetic modification, there exists variability among strains that will impact measured and observed phenotypes, prompting the skilled artisan to question the validity of the phenotype observed.

Endogenous phenotype variability among mice:

The art teaches that that in wild-type C57Bl/6 and 129S1/SvImJ there exists statistically significant differences in grooming behavior (Kalueff AV., 2004, Brain Res., Vol. 1028, pgs. 75-82, see Abstract). Kalueff teaches that both strains are very different behaviorally, including marked strain differences in tests of learning, memory, anxiety, pain responsivity, olfactory discrimination and sensitivity to psychotropic drugs. Overall, C57 mice are non-anxious, more active and good learners. Kalueff continues that in contrast, although numerous 129 mouse substrains show substantial genetic and phenotypic variation, these mice are generally much less active, display more anxiety and their learning varies widely depending on the nature of the task (pg. 75, col. 2 parag 1).

The art summarized above teaches the skilled artisan that at the very basic level, that no two mice are the same phenotypically. This is strengthened more so given the fact that the two strains demonstrated above are some of the most commonly used strains in knockout studies. Given the lack of disclosure of the strain of knockout mouse used in the creation of the claimed mice nor the strain of the mouse ES cell (as detailed below) the skilled artisan would find the claimed knockout mice further unpredictable since the phenotype of schizophrenia observed could result from the background strain used. However, since this information is not disclosed in the specification it will be impossible to know whether the phenotype is due to the genetic background of the mice used to generate the claimed knockout mouse or results from a disruption in Npas3.

Working Examples and Conclusion:

The present specification teaches how the claimed transgenic mouse was made using a Npas3 targeting vector (pg. 10 parag. 0068). A targeting gene construct was made called Targeting Vector for the disrupted Npas3 gene (Fig. 1). The instant specification teaches that correctly targeted ES cells were injected into C57B1/6 recipient blastocyst to obtain chimeric progeny the chimeric mice were bred with C57B1/6 mice to obtain germline transmission of the targeted allele and that heterozygous animals were intercrossed to obtain Npas3 homozygous knockouts that were verified by Northern Blot (pg. 11 parag. 0074). The specification continues to teach that Npas3 KO mice initially appear to develop normal at birth, but shortly after birth the transgenic mice can be distinguished from controls based upon size, with the Npas3 KO mice being smaller (pg. 12 parag. 0078). The specification continues that a battery of behavioral analysis was conduction on the Npas3 KO mice including tail suspension test, footprint test, beam-walking test, locomotor activity test, dopamine pathway locomotor activity test, serotonin pathway locomotor activity test, glutamate pathway locomotor activity test, prepulse inhibition of acoustic startle and zero maze test (pgs. 13-22). However none of these tests or observed results demonstrates that the claimed transgenic knockout Npas3 mouse is a model of schizophrenia. As Picciotto et al. teaches above, there is inherent unpredictability in modeling a schizophrenic mouse and that the skilled artisan must break down individual phenotypes to relate to particular disorders i.e. attention deficit. However the issue with the claimed transgenic and the claimed phenotypes is that they are not predictable to the skilled artisan that the mouse is a model of schizophrenia. Phenotypes such as locomotion, pre-pulse inhibition and maze behavior are highly dependent on the strain of mouse and vary significantly among strains. Phenotypes such as altered responses to glutameric signaling pathways and altered neurotransmitter

signalling pathway are overly broad and do not indicate to the skilled artisan what observed alteration should be prescribed to schizophrenia or schizophrenic behavior. An altered response could be any conceivable observation increase, decrease, or no change and is left entirely up to the interpretation of the skilled artisan. Collectively what the art teaches above is that behavioral phenotypes are unpredictable since 1) they can be dependent on the background strain of mouse and 2) observed phenotypes are difficult to prescribe to complex human diseases such as schizophrenia.

As summarized in the art above, the modeling of schizophrenia in animal models is both complex and unpredictable given the uniquely human nature of schizophrenia. The art further teaches that knockout animal models are unpredictable for a variety of assayed phenotypes, including open-field test and pre-pulse inhibition. Further, the unpredictability of the claimed knockout mouse is emphasized to the skilled artisan in that there is no disclosure of the strain used to make the claimed knockout mouse (only the blastocyst strain is mentioned), this coupled with the teachings in the state of the art of knockout mice above the skilled artisan would be unable to conclude that the phenotypes claimed related to schizophrenia is resulting from the disruption of a Npas3 gene or the background strain of the mouse. The art is very clear as summarized above, that significant variability exists among different strains of mice that are used commonly in knockout studies and with regard to the claim limitation of increased insulin levels in male mice. Further the skilled artisan would not know how to use the mice to determine either a function for the Npas3 gene or how to use results obtained from the mice in the study of or treatment of any particular disease or condition. As the mice have no enabled use, then claims directed to the methods of screening and isolated cells also have no enabled use. Therefore one

skilled in the art, at the time filing, would require an undue amount of experimentation without a predictable degree of success to determine the relationship between the claimed schizophrenia model and subsequent phenotypes in a Npas3 knockout mouse.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is (571)272-3108. The examiner can normally be reached on M-Tr 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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